Modern Concepts of Cardiovascular Disease

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THE MECHANISM OF EDEMA FORMATION

EDEMA is said to be present when the tissues contain abnormal amounts of fluid. With rare exceptions these collections of fluid are intercellular, distending conspicuously tissue spaces which normally are collapsed and contain only minute amounts of tissue fluid. Edema is identified clinically by "pitting on pressure," but this is a relatively crude test since limb volume must be 10 per cent greater than normal before pitting can be demonstrated. Other methods of study can reveal intermediate stages, termed pre-edema or abortive edema, in which the volume of tissue fluid is greater than normal but still not great enough to allow pitting. This gradual transition from normal fluid distribution to gross clinical edema suggests that the factors concerned in producing edema should be sought in perversions of the physiological mechanism which controls the interchange of fluid between the blood capillaries, the tissue spaces and the lymphatic vessels.

Blood flows through the human capillary network under an average pressure head of 32 mm. Hg in the arteriolar portion of the capillaries, falling gradually to 12 mm. Hg in the venous portion. The capillary wall is composed of plate-like endothelial cells which form a thin membrane separating the circulating blood from the tissue spaces. It is generally believed, from chemical and physiological evidence, that the capillary endothelium behaves like a passive (*i.e.*, non-secreting) filtering membrane. Water, salts and simple organic compounds (urea, creatinine, etc.) pass rapidly and easily, but in most situations the plasma proteins, by reason of their colloidal properties, are retained almost completely.

STARLING in 1896 called attention to the fact that those substances which pass through the capillary wall easily (salts, urea, creatinine, etc.) and are present in approximately equal concentration in plasma and tissue fluid cannot exert an osmotic pressure across the capillary wall and cannot, therefore, affect fluid distribution except temporarily. The plasma proteins, however, since they are retained by the capillary wall, develop an osmotic pressure of approximately 26 mm. Hg. This colloid osmotic pressure tends to retain fluid within the capillaries, while capillary pressure tends to filter fluid from the blood.

When capillary pressure exceeds the colloid osmotic pressure of the blood, fluid will be filtered from the blood stream into the tissue spaces. When capillary pressure falls below the colloid osmotic pressure of the blood, fluid will be absorbed from the tissue spaces into the blood stream. The gradient of capillary pressure is balanced against the colloid osmotic pressure of the blood in such a way that under average conditions the filtration occurring in the arteriolar portion of the capillary network is balanced by absorption in the venous capillaries and minute venules. In resting tissues the tendency toward absorption is probably slightly greater than that toward filtration. The amount of tissue fluid is small and lymph flow is minimal.

During muscular activity, however, average capillary pressure is raised considerably above the colloid osmotic pressure by arteriolar dilatation; filtration increases and absorption decreases. Tissue fluid accumulates and passes finally into the lymphatics, hastening the flow of lymph conspicuously. Thus the lymphatics, as one of their functions, conduct excess tissue fluid back to the blood stream by way of the veins when capillary absorption is temporarily reduced. It is evident that the volume of tissue fluid depends normally upon several separate factors. It is to be expected, therefore, that edema can be associated with malfunction of several distinct types.

The factors listed as primary are fundamentally important since each one in sufficient grade can produce edema unaided by other forces. The contributory

Factors favoring edema formation	Clinical examples
A. Primary:	
1. Elevated capillary pressure.	1. (*a*) Venous obstruction. (*b*) Thrombophlebitis. (*c*) Cardiac edema with venous congestion.
2. Lowered colloid osmotic pressure.	2. (*a*) Nutritional edema. (*b*) Nephrotic edema. (*c*) Cardiac edema, late stages with malnutrition.
3. Damage to capillary wall.	3. (*a*) Inflammatory edema. (*b*) Nephritic edema. (*c*) Cardiac edema (?), chronic anoxemia.
4. Lymphatic obstruction.	4. (*a*) Lymphedema. (*b*) Cardiac edema with venous congestion.
B. Contributory:	
5. Low tissue pressure.	5. Edema of periorbital tissues and genitalia.
6. High salt intake.	6. Increases edema if water is available.
7. High fluid intake.	7. Increases edema if salt is available.
8. Warm environment.	8. (*a*) Heat edema. (*b*) Increases all types of edema.
9. Disturbed innervation.	9. (*a*) Tropho-edema. (*b*) Unilateral edema in hemiplegia.

factors, on the other hand, do not themselves ordinarily produce edema, but they often modify the severity or the distribution of edema produced by one or more of the primary causes.

A. Primary Factors.

1. Capillary pressure is elevated whenever venous blood flow is obstructed, *e.g.*, by a tight bandage, by thrombophlebitis, or by the venous congestion of cardiac failure. Average capillary pressure becomes considerably higher than the colloid osmotic pressure of the blood; filtration is abnormally rapid while absorption becomes difficult.

2. Fluid balance is disturbed similarly when the colloid osmotic pressure of the blood is conspicuously less than average capillary pressure. In prolonged protein starvation and in nephrosis the concentration of the plasma proteins is often reduced from the normal 7 per cent to 4 or even 3 per cent. In nephrosis the plasma albumin is reduced especially and the colloid osmotic pressure may be as low as 8 mm. Hg instead of the normal 26 mm. Hg. In advanced cardiac disease with malnutrition mild grades of hypoproteinemia are often associated with moderate venous congestion, the resulting edema being of mixed etiology.

3. After injury the capillary wall becomes permeable to plasma proteins which then lose their power of retaining fluid in the blood stream, since they can no longer exert a colloid osmotic pressure to balance capillary pressure. Inflammatory edemas (*e.g.*, burns, chemical injury) are thus produced; the inflammatory edema fluid contains as much as 5 per cent protein. The edema of acute diffuse glomerulonephritis is ascribed, on indirect evidence, to slight but widespread capillary damage. Anoxemia is known to increase the leakage of protein through the capillary wall and it has, therefore, been suggested, but as yet not proved, that the prolonged slight anoxemia of cardiac decompensation may increase capillary permeability and be partially responsible for cardiac edema.

4. Impaired drainage of lymph, owing to congenital hypoplasia of lymph vessels, to external pressure or to lymphangitis, is responsible for many unilateral collections of fluid. The edema of heart failure has been ascribed in part to obstructed lymph flow because the larger lymphatics must empty their contents into congested veins.

B. Contributory Factors.

5. Extravascular accumulations of fluid separate the tissue elements as the tissue spaces are enlarged. This distention develops in the tissue spaces a pressure which opposes further filtration. Rigid and tightly constructed tissues resist edema formation more effectively than loosely formed tissues. Nutritional, nephrotic and nephritic edemas are frequently observed first in loose tissues (*e.g.*, orbit, face or genitalia) which are easily distensible and in which tissue pressure develops less rapidly.

6. When the body retains 1 liter of water, approximately 9 grams of sodium chloride must be retained simultaneously to prevent dilution of the body fluids. High salt intake facilitates fluid retention and makes latent edema obvious or mild edema more severe. If salt intake be restricted, fluid cannot be retained so easily; mild or moderate edemas of all varieties are more or less amenable to treatment of this type. However, when venous congestion is extreme or when the plasma proteins are very low even rigid salt restriction will be only partially successful. Acid producing salts modify fluid balance significantly, tending to diminish edema by increasing diuresis. Base producing salts, on the contrary, favor fluid retention.

7. A high fluid intake produces edema (*a*) if salt is available and (*b*) if a tendency toward edema exists by reason of one of the primary factors. A salt-poor regime diminishes the amount of water retained even with a high fluid intake.

8. Heat produces peripheral vasodilatation, raises capillary blood pressure conspicuously and, through relaxation of capillaries, increases the area of endothelium available for filtration. Patients frequently observe spontaneously that warm weather and local heat accentuate their edema.

9. In cardiac patients, with latent or mild general edema, hemiplegia is followed at times by conspicuous edema of the paralyzed extremity. Lymph flow, which depends chiefly on muscular activity, is probably retarded by the paralysis. In addition disturbances of innervation often produce temporary or permanent vasodilatation which favors filtration. Disturbances of innervation, however, rarely produce edema unless one of the primary factors is also present in mild grade.

IN SUMMARY, nutritional and nephrotic edemas are uniformly associated with low concentrations of plasma protein and a reduced colloid osmotic pressure of the blood. Capillary permeability and capillary pressure are not increased; it has in fact been suggested recently that permeability is less than normal. The edema fluid generally contains 0.2 per cent protein or less. Ordinarily the tendency toward edema persists until the plasma proteins are 5.5 per cent or more. Occasionally a copious diuresis occurs even in the presence of hypoproteinemia. This occurrence has not as yet been satisfactorily explained.

Nephritic and inflammatory edemas are generally ascribed to slight and conspicuous capillary damage respectively. The edema fluid is said to contain protein in concentrations of 1 per cent or more. Capillary pressure is elevated in inflammatory reactions, but increased capillary permeability is the more important factor.

Cardiac edema is far more complicated. In acute congestive failure edema is ascribed primarily to high capillary pressure and secondarily to venous congestion. Retarded lymph drainage and anoxemia may play a part also. Protracted cardiac decompensation leads to restricted food intake, malnutrition and mild to moderate hypoproteinemia which, in conjunction with venous congestion, often makes late cardiac edema extraordinarily difficult to treat.

This article aims to be merely a schematic outline which, for the sake of clearness and brevity, omits certain qualifying details. Likewise, limited space has made it impossible to list original papers and references.

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